SUPPLEMENT

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ABSTRACTS OF PAPERS PRESENTED
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MONDAY, JUNE 8TH
AND
TUESDAY, JUNE 9TH
1942

SYMPOSIUM

RELATION OF ENDOCRINES TO SKELETAL DEVELOPMENT

1[1]. Genic and Endocrine Determination of Skeletal Development.

W. W. Greulich, *Western Reserve University, Cleveland*

1). The individuality of various centers of ossification as indicated by the rather regular order in which they appear and in which epiphyseal closure occurs.
2). The relation of skeletal status to the menarche in girls and to the attainment of a comparable degree of sexual maturity in adolescent boys.
3). The rapid growth and 'remolding' of the bony pelvis in girls during puberty and early adolescence.
4). Changes in bone density during pregnancy.

2. Cyclic Changes in Blood Calcium and Phosphorus in Relation to Egg Laying.

Oscar Riddle, *Carnegie Institution of Washington, Cold Spring Harbor*

1). The normal cycle in pigeon and fowl, and a concurrent cycle of lipemia.
2). Time relations of increase of blood calcium and bone changes in pigeons.
3). The relative ability of various sterol hormones to induce calcemia and lipemia (amphibians, birds, mammals), and the effect of thyroparathyroidectomy (rat, pigeon).
4). The relative ability of various pituitary hormones to induce calcemia and lipemia, and the role of sex, age, castration and hypophysectomy (birds, mammals).

3. Effect of Sex Hormones on the Skeletons of Birds.

C. A. Pfeiffer, *Yale University School of Medicine, New Haven*

1). Effects of estrogens and androgens upon the skeleton of pigeons with a discussion of the process by which the endosteal hyperossification occurs.
2). Hyperossifications following the administration of sex hormones to the chicken, and the relationship of the parathyroids and the age of the bird in this phenomenon.
3). The differences in skeletal responses to estrogens as exhibited in two breeds of ducks, and the possible correlation with the egg laying capacity of the two breeds.
4). Comparison of the responses of different species of birds (pigeons, chickens, ducks and sparrows) to exogenous estrogens and androgens.

4. Effect of Sex Hormones on the Skeletons of Mice.

W. U. Gardner, *Yale University School of Medicine, New Haven*

1). The effects of various amounts and kinds of estrogens and androgens on the resorption of the pubic bones of mice and on the condition of the rest of the skeleton.
2). Effects of estrogens on the 'breaking strength' of femurs of mice, the organization of the bony lamellae and the chemical composition.
3). Action of estrogen in the absence of the parathyroids.
4). Action of estrogen in the absence of the hypophysis.
5). Some dietary factors in relation to the action of estrogens on osseous tissue.

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[1] Numbers refer to position in program.

5. Influence of Growth Hormone on Skeletal Tissue.

Herbert M. Evans, *University of California, Berkeley*

1). Historical background including gross, roentgenographic, and early histological observations.
2). Effects of growth hormone on the skeleton in normal rats and the effect of hypophysectomy and replacement therapy on the maintenance and repair during the post operative period.
3). Variations in response of animals as influenced by age, dose level and duration of treatment.
4). Assay of growth hormone: skeletal assay vs. gain in body weight. Sensitivity and specificity as determined by body length, x-ray examination and epiphyseal cartilage.
5). Endocrine factors influencing the action of growth hormone, such as thyroid, sex hormones, adrenal cortex and other pituitary hormones (contaminants).

6. Effects of Endocrines on Age Changes in the Epiphyseal and Articular Cartilages.

Martin Silberberg, *New York University, New York City*

1). Skeletal growth and ageing of normal mice.
2). Comparison of the effects of anterior pituitary hormones (extracts and implants), sex hormones (androgen, estrogen, progesterone and of gonadectomy), thyroid hormone and potassium iodide on the age changes in the epiphyseal and articular cartilage in rodents.
3). Effects of combined administration of various hormones (estrogen and anterior pituitary extracts, estrogen and thyroxin, estrogen and progesterone, estrogen and testosterone) on the epiphyseal and articular tissues.
4). The significance of the age factor in the response of the skeletal tissues to hormones.

7. The Effect of Estradiol Benzoate and of Testosterone Propionate and of Combinations of Both on Postmenopausal Osteoporosis and Senile Osteoporosis.

Edward C. Reifenstein, Jr., F. Albright, W. Parson and E. Bloomberg, *Massachusetts General Hospital, Boston*

1). A definition of osteoporosis.
2). A classification of the causes of osteoporosis.
3). The effect of estrin therapy on osteoporosis.
4). The effect of testosterone therapy on osteoporosis
5). The effect of both estrin and testosterone on osteoporosis.
6). The mode of action of estrin as opposed to the mode of action of testosterone.

8. Lack of Effect of Parathyroid Glands on Growth of Bone.

Joseph C. Aub, *Harvard Medical School, Boston*

1), Presentation of a case of a parathyroid tumor in a growing boy showing differentiation between decalcification of the shaft of the bone with great calcification in the areas of growth.
2). Growth of the antlers of deer with no evidence of parathyroid overactivity.
3). From the above the activity of osteoblasts will be discussed with respect to their independence of parathyroid control.

9. A Conception of the Mode of Action of the Parathyroid Hormone.

Fuller Albright, *Massachusetts General Hospital, Boston*

1). Calcium-phosphorus equilibrium in the isoparathyroid state.
2). The four cardinal metabolic changes produced by the parathyroid hormone.
3). The author's interpretation of the relationships, one to another, of these four changes.

53.[1] ENDOCRINE ASPECTS OF A SOLID OVARIAN TUMOR ASSOCIATED WITH ADRENO-GENITAL SYNDROME AND POLYCYTHEMIA

A. R. ABARBANEL AND H. C. FALK. *Department of Gynecology, Harlem Hospital New York City*

A case is reported of a 22-year-old female who developed seconday amenorrhoea at the age of 16, followed by hirsutism, deepening of the voice, and enlargement of the clitoris. Following operative removal of the ovarian tumor, menses returned 28 days later, hirsutism markedly decreased, while the voice grew lighter. Preoperative and postoperative studies included blood chemistry, urine and hormonal studies, both biological and chemical. Preoperatively, the urine yielded steroids of the androstane, androstene, and pregnane group. 17-ketosteroids, colorimetrically, were 40 mg. equivalents of androsterone per liter. Biological assay also revealed a high androgenic titer. Preoperative creatine retention, using creatine tolerance test, was 92%, while postoperatively it fell to around 50%. Vaginal smears were very atrophic but beginning 8 days postoperative, the smears (new Shorr technique) showed increasingly more estrogenic influence. Vaginal PH rose from 7 to 4.5. Biopsies of endometrium and cervix revealed an almost atrophic condition. Three weeks postoperatively, biopsies demonstrated a strong estrogenic (proliferative) response.

36. STUDIES ON THE ASSAY OF PITUITARY GONADOTROPINS USING THE AUGMENTATION REACTION

R. W. BATES AND J. P. SCHOOLEY. *Difco Laboratories Incorporated, Detroit*

The ratios of chorionic to pituitary gonadotropin were varied systematically in studies with immature female rats. When the ovarian weights are plotted against the logarithm of the dose of either chorionic, FSH, or combinations thereof, straight lines of characteristic slopes may be passed through the experimental points. The slopes of such lines were found to be a function of the relative proportions of FSH to LH or to chorionic gonadotropin in the sample tested.

When FSH dosage was kept constant and chorionic dosage was varied, it was found that after an early rise in ovarian weight a region of no change of ovarian weight with increasing chorionic dosage occurred between dose levels of 1 to 10 I.U., irrespective of the FSH level. At higher dosage levels of chorionic than 10 I.U. the ovarian weight again increased rapidly. This circumstance makes possible the accurate assay of FSH potency by the combination of the pituitary fraction under test with 3 I.U. of chorionic gonadotropin. This level is selected because it falls in the middle of the plateau region and because it does not increase ovarian weight significantly when given alone. Remarkably consistent and potentiated ovarian weight responses to variable dosage of FSH were obtained in the ovarian weight region between 20 and 50 mg.

[1] Numbers refer to position in program.

54. GERONTOTHERAPY, A NEW CONCEPT

HARRY BENJAMIN. *New York*

Gerontotherapy is a new term. It indicates the treatment of the aging process as an entity. While geriatrics deals with the management of the diseases incident to old age, gerontotherapy attempts to influence senescence and senility as such. The attempt is made to diagnose endocrine deficiencies, even those of mild degree, by clinical and laboratory methods. The endocrine constitution of the aging patient is likewise taken into consideration. The corresponding treatment is then administered or added to those measures which are dictated by the demands of geriatric considerations.

10. EXPERIMENTAL MODIFICATION OF MOLTS AND COAT-COLOR CHANGES BY CONTROLLED LIGHTING OF THE BONAPARTE WEASEL (*Mustela cicognanii cicognanii* Bonaparte)

THOMAS HUME BISSONNETTE AND EARL ELMORE BAILEY. *Trinity College, Hartford*

For three years, two Bonaparte weasels, similarly fed and cared for, at temperatures of 40–70°F., were alternately subjected to controlled daily periods of available light. Both maintained normal molts and color cycles on normal light cycles. Normal pelt cycles were resumed upon return to normal days after experimental manipulations. Molting and more or less growth of white pelt followed shortened daily light periods, even in March and April, when control on normal days turned brown. One passed a summer in piebald coat, after incomplete color change in both directions, and in almost complete white the next summer, followed by complete white, after autumn molt on normal days, and returned to brown in spring. One whitened in October, on short days, and returned to brown in December, on long days. The other responded likewise under similar manipulation. Gradually or suddenly shortened days induced white, lengthened days, brown, regardless of previous color. Molting stopped short of completion following appropriate changes of lighting. Temperature change was not a major factor conditioning these molts and color changes. Changes of daily lighting constituted the major factor inducing and controlling molts and color changes in these Pennsylvania-bred weasels studied in Connecticut.

44. An Evaluation of Urinary 17-Ketosteroid Estimations Determined by an Aqueous Modification of the Zimmermann Reaction

James B. Black, Jr. *Barbara Henry Research Laboratory of the New York Hospital and the Department of Medicine, Cornell University Medical College, New York*

The crude neutral and ketonic neutral fractions of 84 specimens of urine collected during consecutive 24-hour periods from 6 normal men have been qualitatively and quantitatively analyzed for 17-ketosteroid content by the Holtorff-Koch modification of the Zimmermann reaction. Extinction-coefficient ratios have been determined for each fraction of each specimen and evaluated in their serial and interfractional relationships. These qualitative indices have also been correlated with quantitative values expressed as I.U. Androsterone equivalents determined for each fraction of each specimen.

The results conclusively showed that variously colored non-ketosteroid chromogenic substances contributed significantly to the titers of all the crude neutral urine extracts, and that the presence or absence of these substances could not be determined by observation of extinction coefficient ratios. These findings signify that any use of correction factors dependent on such indices is untenable, and that estimations of 24-hour values should be made on ketonic extracts to be reliable. Serially determined 24-hour ketonic values for individuals observed under controlled standardized conditions proved remarkably constant in this study.

28. Responses of Laboratory Animals to a New Synthetic Estrogen

Ernest W. Blanchard. *Research Laboratories, Schieffelin & Company, New York City*

The physiological and histological effects of 2,4-di(parahydroxy phenyl)-3-ethyl hexane, #118B, a synthetic estrogen, have been studied in detail in an effort to determine its action and relative 'toxicity.' The compound has been administered at various levels, by various routes, to several groups of rats. Daily weight changes, food intake, gross changes, and vaginal smears were noted. Sample animals from the groups were autopsied at monthly intervals and the gross, histological and —in the case of the hypophysis—cytological appearance of the essential organs studied. Castrate mature female rabbits were primed with this material in preparation for progesterone injection.

Physiologically, the compound behaves as do the natural estrogens, except that it is highly active by mouth. With continuous administration at the higher levels certain modifications in some organs occur which are identical with those which follow similar treatment with estrone and estradiol. The 'toxicity' was less with '118B' than with the natural and synthetic estrogens studied. (*See also abstract 28A, Steblims and Blanchard*)

1. Metabolic Changes in Co-existing Diabetes Mellitus and Addison's Disease

B. D. Bowen, G. F. Koepf, Grosvenor Bissell and Donald Hall. *Department of Medicine, University of Buffalo School of Medicine and the Metabolic Division of the Buffalo General Hospital, Buffalo*

It has been shown by Long and Lukens that adrenalectomy attenuates diabetes induced by pancreatectomy in the cat. Co-existing diabetes and Addison's disease is extremely rare and unequivocal evidence as to its existence is offered in only 4 cases. In the present instance the diabetogenic properties of the adrenal cortical hormone were studied in a patient with diabetes mellitus, hypertension and pulmonary tuberculosis who subsequently developed Addison's disease. The following changes were noted. *a*). A drop in blood-sugar level and disappearance of glycosuria coincidental with the onset of Addison's disease. *b*). A return of the previous high blood-sugar level after treatment with adrenal cortical extract, but not after desoxycorticosterone acetate therapy. *c*). Disappearance of the hypertensive state coincidental with the development of an Addisonian crisis. After desoxycorticosterone acetate therapy the hypertension recurred. *d*). Characteristic blood electrolyte changes of Addison's disease with the exception of a low CO_2 combining power. *e*). Autopsy findings of a small pancreas (80 gm.), caseous tuberculosis of both adrenal glands, pulmonary tuberculosis, tuberculous pericarditis and diabetic nephropathy.

These studies indicate that lack of the adrenal cortical hormone attenuates diabetes mellitus in the human.

4. Effects of Hypothalmic Lesions and of Subtotal Sympathectomies on Menstrual and Ovulatory Cycles of the Monkey (*Macaca mulatta*)

Chandler McC. Brooks and Philip Bard. *The Johns Hopkins University School of Medicine, Baltimore*

The following results were obtained in a study of 4 immature and 16 mature monkeys. Neither bilateral ablation of stellate ganglia (2 animals) nor bilateral removal of superior cervical ganglia, abdominal sympathetic chains and coeliac ganglia (3 animals) abolished the rhythm of catamenia or the regular occurrence of signs of ovulation. In 2 immature animals, transection of the

hypophysial stalk with ablation of the lower portion of the tuber cinereum prevented sexual maturation, but failure of growth suggested hypophysial impairment. Three mature monkeys which had had normal cycles showed complete absence of cycles following similar lesions. In 4 mature females *practically* complete section of the hypophysial stem was accomplished. These animals, after several months during which menstruation did not occur, began to ovulate and menstruate regularly, although the cycles were 36 to 42 days in duration. It appears that complete integrity of hypothalamico-hypophysial connections is not essential for the occurrence of the cycles.

Diabetes insipidus and menstrual abnormalities were commonly, although not invariably, associated in this series. Hypothalamic lesions confined to the suprachiasmatic area and to the anterodorsal portion of the tuber (4 animals) produced obesity and a progressive deterioration of the rhythmicity of menstruation and ovulation.

7. Excretion of Estrogen in Bile

A. Cantarow, A. E. Rakoff, K. E. Paschkis and L. P. Hansen. *Departments of Medicine, Obstetrics and Biochemistry, Jefferson Medical College, Philadelphia*

Studies were made of the excretion of estrogen in the bile of cholecystectomized, bile-fistula, female dogs, the bile draining into a balloon. No estrogenic activity was present in the bile of untreated animals. Following a single intravenous injection of 250,000 I.U. of estrone in alcohol, the level of blood estrogenic activity after 4 hours is about 10% of that at 10 minutes, falling to practically zero after 24 hours; about 10% is recovered in the urine during the first 24 hours, the quantity diminishing during the next 3 days. Bile excreted during the first 24 hours contained substances exhibiting 40–48% of the estrogenic activity of the injected estrone. If no bile was re-fed, approximately the same quantity was excreted in the second 24 hours. When 75% of the bile was re-fed at the end of each 24-hour period, about 26% was excreted during the second and a similar quantity during the third day. These observations suggest the existence of an enterohepatic circulation of estrogens, similar to that of bile acids, and throw some doubt upon the hypothesis of rapid destruction or inactivation of estrogens by the liver in intact animals.

41. Choline Esterase Activity of Blood Serum in Patients with Endocrine Disease

O. Cope, O. Krayer and F. Plachte. *Departments of Surgery and Pharmacology of the Harvard Medical School and the Massachusetts General Hospital, Boston*

The choline-esterase activity of the blood serum has been investigated in patients with various endocrine disturbances and in dogs following adrenalectomy. In 6 patients with hyperparathyroidism the levels of activity were distributed in the high range. Following resection of the parathyroid tumor, the choline-esterase activity fell simultaneously with the blood calcium level; the changes were not absolutely equivalent. A patient with a preoperative calcium level of 17 mg./100 cc., which descended to 7 mg. after operation, showed no greater drop in choline-esterase activity than another whose calcium went from 14 to 9 mg. A patient in Addisonian crisis had a high choline-esterase activity. After adequate treatment with adrenal cortical extract and salt, the activity fell to a mid-normal level. The patient was placed on a dose of desoxycorticosterone acetate sufficient to maintain normal electrolyte balance but the choline-esterase activity rose. Upon administration of extract for the second time, the activity fell. Desoxycorticosterone pellets were then implanted; the activity again rose.

Five dogs were studied before and after adrenalectomy. In 2 the activity rose, in 1 there was no change, and in 2 it fell. The changes were sufficient to be significant.

The serum choline esterase activity was also observed in patients with myxedema and thyrotoxicosis, and in normal individuals.

57. Metabolic Effects of Testosterone Implants

Joseph Eidelsberg, Maurice Bruger and Mack Lipkin. *New York City*

As noted previously by other observers, a reduction in the urinary excretion of nitrogen, chlorides and phosphates was observed following the injections of testosterone propionate. Implanted pellets of testosterone may initiate and maintain the reduced excretion of these components during a period which closely coincides with that of the clinical response. These observations suggest that the effective life of a testosterone implant may be demonstrated by the urinary excretion of nitrogen, chlorides and phosphates.

22. Further Studies of the Relationship of Progesterone to the Induction of Ovulation in the Persistent-Estrous Rat

John W. Everett. *Department of Anatomy, Duke University School of Medicine, Durham*

Progesterone, administered in daily doses of 0.25 to 1.0 mg., was previously shown to have temporarily restored regular ovulatory cycles to persistent-estrous rats. The hormone seemed especially to be required at or near proestrus. This question is now explored further. After an initial dose of progesterone which served merely to interrupt

persistent estrus without inducing ovulation (>95%), a second isolated injection has been given on various specific days of the subsequent diestrus interval or of the following estrous period. The effectiveness of the treatment in producing ovulation is slight (circa 30%) early in diestrous, rises to a maximum (60–70%) on the first day of estrus (Stages I or II) and then falls gradually to a negligible value when estrus has persisted longer than 7 days. Sequences of apparently normal cycles can be produced simply by giving progesterone on the first day of each estrous period; if the treatment is withheld at any time, the current set of follicles will persist. The implications of these observations is discussed with reference to current theory of the estrous cycle.

39. Genital Atrophy During Pantothenic Acid Deficiency and Responses to Gonadotropic and Estrogenic Hormones

F. H. J. Figge and Edgar Allen. *Departments of Anatomy, University of Maryland, Baltimore, and Yale University School of Medicine, New Haven*

Female rats maintained from weaning on diets deficient in pantothenic acid had infantile genital organs up to 75 days of age. The experiment was repeated with 60 additional female rats, 36 being placed on pantothenic-acid-deficient diets, and 24 controls maintained on the same diet plus pantothenic acid. In 35 of the 36 animals on deficient diets, the vagina had not opened at the age of 88 days. In the 24 controls the vagina opened between 40 and 45 days of age and cornified smears indicated regular estrous cycles at intervals of 4 to 6 days.

The genital organs of the pantothenic deficient animals were extremely atrophic. The vaginal epithelium was only 2 layers thick and the uterus was tiny and anemic. Both organs were even more atrophic than after ovariectomy. Study of the ovaries in most cases showed failure of ovulation. The largest follicles were of medium size and similar to those of hypophysectomized animals. The ova frequently had zones of vacuolated cytoplasm, as described by Marrian and Parkes for vitamin B deficiency. In some animals 1 or occasionally 2 sets of corpora lutea were present. Some of these corpora had a 'moth eaten' appearance, similar to those described by Pfeiffer in constant-estrous animals. These ovaries, though ovulating once or twice, were extremely underdeveloped when compared to those of the controls.

Gonadotropic and estrogenic hormones were injected into the animals on pantothenic acid deficiency and typical responses were obtained at the expected times. Other symptoms of deficiency were not greatly affected.

34. Present Status of Male Sex Hormones and the Chorionic Gonadotropins as Growth Stimulating Factors

Rita S. Finkler, Nathaniel J. Furst and George M. Cohn. *Departments of Endocrinology and Roentgenology of the Newark Beth Israel Hospital, Newark*

A group of 58 children was treated at the Endocrine Clinic of the Newark Beth Israel Hospital during the last 8 years for growth deficiency alone or in combination with genital retardation. The following hormones were employed either singly or in combination depending upon the outstanding feature of the deficiencies: thyroid, anterior pituitary gland extracts, chorionic gonadotropins and testosterone compounds. An initial period of observation was made during which time we attempted to evaluate the nutritional and thyroid elements. The results obtained were variable. X-ray studies did not show definite or demonstrable changes in the majority of cases; clinically, best results were obtained in those cases which presented a combination of growth and genital retardation; improvement in genital status was accompanied by an increase in growth increment.

55. Relationship of Serum Cholesterol to Total Body Cholesterol in Experimental Hyper- and Hypothyroidism

Walter Fleischmann and Harris B. Schumacker, Jr. *Department of Pediatrics and Surgical Hunterian Laboratory, Johns Hopkins University School of Medicine, Baltimore*

Sterol balance studies on cretins have shown that the characteristic changes in the concentration of serum cholesterol associated with the institution or withdrawal of thyroid therapy occur even when the patients are on diets very low in cholesterol. It was also found that these serum cholesterol changes are not due to changes in cholesterol excretion. (Fleischmann and Wilkins). The experiments to be reported here were made to decide whether the thyroid hormone influences the distribution of cholesterol between blood plasma and the body tissues or cholesterol synthesis and destruction. Total body cholesterol and serm cholesterol were determined in thyroidectomized rabbits and rats, in rats treated with thyroxin and in normal controls. It was found that the cholesterol content of the serum does not reflect the total body cholesterol. For instance, the total body cholesterol content was the same (0.16% of body weight) in thyroidectomized rabbits (average serum cholesterol 223 mg.%) and in normal rabbits of the same weight (average serum cholesterol 92 mg.%). The experimental material presented suggests that the thyroid hormone influences the shift of cholesterol to and from the blood plasma rather than that it has a specific effect on cholesterol metabolism.

30. THERAPEUTIC USE OF DIETHYLSTILBESTROL DIPALMITATE

S. C. FREED, W. M. EISEN AND J. P. GREENHILL. *Loyola University School of Medicine, Chicago*

In the castrate rat the minimal effective estrous dose of oil solutions of diethylstilbestrol dipalmitate is about 1/50 that of diethylstilbestrol and about 1/10 that of diethylstilbestrol dipropionate. This relationship of activities is probably due to the different rates of absorption of these compounds from the site of injection. We have assayed these substances in the human, using the relief of menopausal symptoms as the criterion of activity. Our results demonstrate that, in contrast to the assays in animals, diethylstilbestrol dipalmitate is more effective than either the dipropionate or the free compound in giving not only greater relief but in maintaining this condition over a longer period of time following cessation of therapy. These results indicate once more the limitations of animal assays of estrogens in the establishment of therapeutic standards and the necessity of using the human as the final test of estrogenic efficiency. In addition, the administration of the dipalmitate rarely gave rise to side reactions although equal quantities of the free compound induced a high incidence of such reactions while the dipropionate brought forth a lesser but still significant incidence of unpleasant symptoms.

56. THE 'SPONTANEOUS' VARIABILITY OF THE ORAL GLUCOSE TOLERANCE

H. FREEMAN, J. M. LOONEY AND R. G. HOSKINS. *The Memorial Foundation for Neuro-Endocrine Research, Worcester State Hospital, Worcester*

The oral glucose tolerance test was investigated as a possible diagnostic feature for endocrinopathic conditions. Repetitions for the procedure showed marked inconsistency in the curves. A review of the literature revealed that there have been few investigations in normal subjects of the consistency of this test. The material was therefore enlarged to include a total of 35 healthy male subjects in whom duplicate determinations were made within a short time. Analysis of the data showed that the average variation in the fasting levels of blood sugar between the two tests was 9 mg. per cent and extended to 30 mg. at the one-hour reading with a maximum deviation at this point up to 90 mg. The relationship between the fasting, half-hour, hour and two-hour readings, respectively, in the two tests was very slight, the one-hour reading showing the highest co-variance. This inconsistency was not improved by comparing either the maximum levels attained in the two tests or the maximum increase in the blood sugar, irrespective of time. The variability of the test is so great that it has slight diagnostic value except in diabetes mellitus.

47. DIFFERENTIAL DIAGNOSIS OF VIRILISM WITH SPECIAL REFERENCE TO PSEUDOHERMAPHRODITISM

HARRY B. FRIEDGOOD. *Medical Clinic, Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston*

In a syndrome of such varied origins as virilism the differential diagnosis is particularly important from the viewpoint of therapy. The urinary excretion of 17-ketosteroids (17-KS) has been of significant aid in this matter. On the average, normal women excrete the equivalent of 8 to 10 mg. of androsterone per 24 hours as determined by the Zimmermann reaction (absolute alcohol technique); the range of 17-KS excretion in uncomplicated hypertrichosis (hirsutism) is usually within normal limits. The 17-KS in virilistic patients (except those with adrenocortical tumor) ranges from the normal to 35 or 40 mg. per 24 hours. The total 24-hour urinary 17-KS excretion is above 45 mg. equivalents of crystalline androsterone in cases of virilizing adrenocortical tumor. Two cases of adrenocortical hyperplasia have been encountered, however, in which the 17-KS excretion equaled that found in tumor cases. In one of these, a striking example of pseudohermaphroditism, the 24-hour 17-KS excretion averaged 85 mg. preoperatively. Thus it is not the total 24-hour 17-KS excretion which is of differential diagnostic significance. A differential point was found, however, in the determination of the α and β-steroids which disclosed that the latter constituted less than 17% of the total 17-KS excreted by the patients with adrenocortical hyperplasia, whereas in the virilizing adrenocortical tumors the β-steroid fraction accounted for more than half of the total 17-KS excreted.

The patient with pseudohermaphroditism was treated surgically by removal of the entire right adrenal and ⅓ of the left adrenal. The 17-KS excretion decreased to an average of 31 mg., the 24-hour estrogen increased from a preoperative average of 2.6 μg. estrone to 8.5 μg. within 2 months. Postoperatively, the vaginal smear showed increasing evidence of cornification, the breasts began to grow, the huge clitoris decreased in size and her masculine habitus became partially feminized. She died accidentally of adrenal insufficiency 3 months after operation.

14. THE 'CORTICOMIMETIC' ACTION OF STILBESTROL ON CARBOHYDRATE AND PROTEIN METABOLISM

E. G. FRY, M. MILLER AND C. N. H. LONG. *Department of Physiological Chemistry, School of Medicine, Yale University, New Haven*

Since there is considerable evidence that estrogens when administered over a period of days

cause hypophyseal and suprarenal hypertrophy, accompanied by elevated carbohydrate levels in the blood and tissues, the synthetic estrogen, 4:4′ dihydroxy-diethyl stilbene, in the present experiments was given to 24-hour-fasted male rats to compare effects of this compound with those produced by adrenal cortical steroids.

Thirty hours after the injection of stilbestrol (5 mg. per 100 gm. body weight) in sesame oil, weight loss, urinary nitrogen and potassium excretion, liver glycogen, liver protein, blood sugar and serum potassium values were significantly greater than in the oil-injected controls. The same dose of stilbestrol did not elicit this response immediately after adrenalectomy regardless as to whether the animals were injected with physiological saline or implanted with pellets of desoxycorticosterone acetate. In the absence of the hypophysis, injections of the estrogen likewise failed to increase the liver glycogen or the nitrogen excretion.

The results indicate that the effect of stilbestrol, and probably other estrogens, in increasing the carbohydrate levels and nitrogen excretion of fasted rats is brought about by increased secretory activity of the anterior pituitary which augments hormonal production of the adrenal cortex.

58. Effects of Prolactin and of Prolactin-Free Pituitary Extracts on the Spleen

Max. A. Goldzieher, Irving Sherman and Bernard Sherman. *New York City*

Young male rats were given daily injections of prolactin and prolactin-free gonadotropic anterior lobe extracts at different dosage levels. The animals were killed on the tenth day and the weight of the spleen compared with that of the controls. In one set of experiments, injections of prolactin were given while in others extracts made according to Perla, or extracts made practically free of prolactin by isoelectric precipitation, were used. The splenic weight increased both after injection of the Perla extract and upon use of our prolactin-free gonadotropic extract. Injections of prolactin, on the other hand, decreased the weight of the spleen.

Histologic examination showed that the gonadotropic extract caused considerable congestion of the splenic pulp accompanied by reduction in the volume of the lymphatic apparatus, especially of the halo-like zone which surrounds the Malpighian bodies. The megakaryocytes of the splenic pulp showed pyknosis, or lysis of their nuclei with accompanying changes of their cytoplasm. The spleen of the animals injected with prolactin showed considerable enlargement of the perifollicular zone and an increase in the number and size of the reticulum cells of the splenic pulp. The megakaryocytes appeared to be numerous; their nuclei healthy and without the changes noted in the other experiment. Following a single injection of the gonadotropic extract, the polynuclear leucocytes increase and reach a peak within 2 hours. A substantial decrease in lymphocytes and a slight increase in monocytes is concomitant. Animals injected daily for 10 days with the gonadotropic solution showed a considerable drop in the number of polynuclears, an increase in lymphocytes and a substantial drop in monocytes. Injections of prolactin do not substantially alter the blood count.

38. Mammary Gland Growths in Hypophysectomized-Castrated Guinea Pigs

E. T. Gomez. *Division of Nutrition and Physiology, Bureau of Dairy Industry, United States Department of Agriculture, Washington*

Growth of the duct system of the mammary glands of hypophysectomized-castrated male or female guinea pigs has been induced by implanting or injecting a total of 20–50 mg. of macerated fresh prehypophyseal glands of male or female guinea pigs in saline suspension apportioned over a period of 10 days. Injections of the total amount of material obtained by extracting 20–50 mg. of fresh prehypophyseal (guinea pig's) glands with a mixture of alcohol and ether apportioned in 10 daily administrations resulted in growth of the mammary glands, equalling that of early pregnancy, in hypophysectomized-castrated guinea pigs of either sex. The extract showed no reparative effect upon the atrophied thyroids and adrenals; there was no body-growth-promoting effect and in the females, cornification of the vaginal epithelium was not manifest. Relatively purified lactogenic hormone (10 mg.) administered daily for 10 to 15 days, either alone or in combination with estrone (75 I.U.), progesterone (5 mg.), or desoxycorticosterone (5 mg.) did not cause growth of the mammary glands.

Treatments of all operated animals were started 60 to 100 days after hypophysectomy. The mammary gland growth was determined by study of the whole mounts of stained and dissected glands.

32. Synergism Between Pituitary Extracts and Chorionic Gonadotropin

Harry A. Gusman, *Cleveland*, and Max. A. Goldzieher. *New York City*

In continuation of previously published work, the synergistic effect of vatious pituitary fractions was investigated. These anterior pituitary fractions included prolactin, adrenotropin, thyrotropin and a 'growth hormone' extract. The effect of these extracts on the ovaries and uteri of infantile rats was tested, alone and in combination with chorionic gonadotropin in subminimal dosage. All the extracts used alone were ineffective. With added chorionic gonadotropin, considerable increase of uterine

weight was obtained which was greatest in the prolactin and adrenotropin experiments, smaller but of definitely significant extent in the thyrotropin and growth-hormone experiments. The ovarian weights were not significantly increased. Combination of prolactin and adrenotropin gave the greatest uterine weight, whereas addition of thyrotropin to the combination gave by far the smallest increase.

Histological examination of the uteri showed changes entirely comparable to those obtained with the crude anterior lobe extracts or the specific metabolic principle combined with chorionic gonadotropin. The ovaries, however, did not show enlargement and ripening of the follicles; luteinization of one or two follicles could be noted.

The synergistic effect of unfractionated anterior lobe extracts is due, not only to the presence of the specific metabolic principle as previously shown, but also to the various organotropic or growth-promoting fractions present.

8. MALE HORMONE STIMULATION IS PREREQUISITE AND AN INCITANT IN COMMON BALDNESS

JAMES B. HAMILTON, *Department of Anatomy, Yale University School of Medicine, New Haven*

The etiology of common baldness was studied experimentally in men with testicular insufficiency, namely: 10 eunuchoids; 94 eunuchs, 10 of whom had been castrated prepubertally, 34 bilaterally orchidectomized during adolescence, and 50 castrated as adults. Common baldness never appeared in the 54 men who did not mature sexually. This is scarcely fortuitous in view of the *a*), genetic predisposition to alopecia in some of these men as indicated by tendencies to become bald when provided with exogenous androgens and by the prevalence of baldness among normal male relatives; *b*), high incidence of some hair loss in normal men, 43 per cent according to Snyder and Yingling. Concomitantly, the amount of dandruff and sebaceous secretion was less in castrates than in normal men.

Male hormone treatment of 12 of these castrate and eunuchoid men, providing stimulation considered equivalent to that in normal men, resulted in increased sebaceous secretions, acne, dandruff, and 4 instances of baldness in a pattern observed in normal men. Progressive loss of head hair ceased when androgenic medication was discontinued in 2 cases, recommenced upon further therapy. Castration of men becoming bald prevented progression of alopecia but promoted no general regrowth of hair on bald areas.

Pedigrees of patients receiving testosterone compounds suggest that a genetic predisposition and male hormone stimulation are necessary to development of common baldness.

9. THE RELATION OF GONADOTROPIC HORMONE TO OÖPHORECTOMY, CLIMACTERIC SYMPTOMS AND DIETHYLSTILBESTROL THERAPY IN WOMEN

CARL G. HELLER, JACOB P. FARNEY, DONALD N. MORGAN AND GORDON B. MYERS. *Wayne University College of Medicine, Detroit*

Urinary gonadotropic hormone excretion was studied before and after oöphorectomy in 27 women with chronic pelvic inflammatory disease. The alcohol-dialysis-alcohol-precipitation method was used to concentrate the 12-hour over-night specimens. The uterine and ovarian weight increases in immature rats were used as a quantitative assay criterion.

Eleven women had high gonadotropic titers preoperatively, probably associated with oöphoritis. All 16 women, who exhibited low or only slightly increased titers preoperatively, showed peak excretion within 6 to 10 days after operation. Climacteric symptoms did not develop before the fourth postoperative week, and as a rule appeared earlier in those women with lower preoperative gonadotropic titers. Four that did not develop symptoms had high preoperative titers. This seemed to indicate that symptoms were related to estrogen withdrawal.

Oral diethylstilbestrol therapy was instituted after repeated assays showed that gonadotropic titers had reached a high stationary level, and climacteric symptoms were troublesome. In the majority of patients, satisfactory symptomatic relief was afforded by 0.5 mg. of diethylstilbestrol daily. In 3, it was necessary to increase the dose to 1 mg. daily. Diethylstilbestrol in these doses did not inhibit urinary excretion of gonadotropins. There was no relation between climacteric symptoms and gonadotropic excretion.

59. ADDITIVE EFFECTS OF INSULIN HYPOGLYCEMIA AND ANOXIA

H. E. HIMWICH, J. F. FAZEKAS, H. C. HERRLICH AND EDITH RICH. *Department of Physiology and Pharmacology, Albany Medical College, Union University, Albany*

Normal concentrations of glucose and oxygen in the blood are necessary requirements for the adequate supply of cerebral energy. In the present experiments the combined effects of insulin hypoglycemia and anoxia on cerebral metabolism and the survival period of dogs anesthetized with Dial were studied. The persistence of respiratory movements was used as a criterion of survival. The average cerebral arterio-venous oxygen difference after insulin diminished from 8.46 to 3.80 volumes % when blood sugar fell below 22 mg.%. With 8% oxygen a gradual decrease of the cerebral arterio-venous oxygen difference was observed in animals surviving for at least 4 hours. When the cerebral arterio-venous oxygen difference was still

within normal limits, during hypoglycemia, the respiration of 8% oxygen caused a rapid decrease in the arterio-venous oxygen difference and shortened the average survival time to 23 minutes. Either the administration of glucose intravenously or the substitution of air for the 8% oxygen mixture permitted the re-establishment of normal respiratory movements.

25. Effects of Sex Hormones upon Hair and Sebaceous Glands in the Rat

Charles W. Hooker and Carroll A. Pfeiffer. *Department of Anatomy, Yale University School of Medicine, New Haven*

Subcutaneous injection twice weekly for as long as 8 months of 83 μg. of estradiol benzoate to male and female rats resulted in loss of body hair. Regrowth of hair in shaved areas required approximately one-third as much time in untreated rats as in the animals receiving the estrogen. Supplementing the diet of the treated animals with cystine or casein did not offset or prevent the inhibition of hair-growth by estrogen. When 1.25 mg. of testosterone propionate was administered simultaneously with the estrogen the regrowth of hair was essentially like that of untreated rats. The sebaceous glands of the animals receiving the estrogen were markedly atrophic and greatly reduced in number. The atrophy of sebaceous glands was entirely prevented in the animals receiving the androgen along with the estrogen, and these structures were often larger than in untreated rats. Moreover, in the estrogen-treated animals receiving cystine the effect of the estrogen upon the sebaceous glands was significantly less marked. The inhibition of body growth in the estrogen-treated animals was not prevented by increased cystine intake. Body growth in the animals receiving the androgen in addition to the estrogen was not as great as in untreated rats, but considerably exceeded that in the animals receiving estrogen alone.

42. A Rapid Assay for Adrenal Cortical Hormone

Chester Hyman and Robert Chambers. *Department of Biology, Washington Square College, New York City*

The edema rate in a Lewen-Trendelenberg preparation of frog's legs was found to diminish when adrenal cortical extracts were added to the various perfusion media. This effect may be applied to the rapid, quantitative determination of the edema-preventing property of adrenal cortical hormone. In this manner concentrations of commercial extract as low as 0.001% may easily be detected. The relation between the life-maintenance assay as reported by the manufacturer and that of the edema-preventing property of various extracts and fractions has been tested.

6. Prevention of Jejunal Ulcer by Enterogastrone

A. C. Ivy. *Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago*

Ten of 35 Mann-Williamson dogs received intravenously 3 times daily an extract of pork muscle prepared by the method for preparing enterogastrone. The remaining received enterogastrone. All the animals receiving muscle extract developed ulcer. Only 6 of the 25 receiving enterogastrone developed ulcer. These data show that the enterogastrone extract employed, even though impure and known to produce refractoriness in about 25% of dogs, had a remarkable potency in preventing the development of jejunal ulcer.

11. On the Specificity of Certain Physiological Reactions

H. Jensen. *Research Laboratories. The Upjohn Company, Kalamazoo*

In order to evaluate correctly the pharmacodynamic response elicited on parenteral administration of comparatively crude organ and tissue extracts, a distinction between specific and non-specific physiological effects must be made. Frequently a response observed with rather impure preparations has been considered as being specific and has therefore been attributed to the function of a distinct agent present in the extract. However, a more thorough pharmacological investigation of such preparations has often shown that the effect observed was non-specific and the assumption of a separate specific factor therefore unnecessary. Certain recent physiological observations from the point of view of specific and non-specific effects are discussed: *a*), the anti-insulin and ketogenic effects of the anterior pituitary; *b*), the presence of insulin-like substances in the urine; and *c*), the non-specific response of tissue extracts on blood pressure, with special reference to the anti-hypertensive action of kidney extracts.

2. Two New Procedures to Assist in the Recognition and Exclusion of Addison's Disease

Edwin J. Kepler, Marschelle H. Power and Francis J. Robinson. *The Mayo Clinic and The Mayo Foundation, Rochester*

Patients who have Addison's disease do not experience normal diuresis after ingesting water. In addition, there are disturbances in clearances of urea and chlorides. These phenomena have been utilized as the basis for two comparatively simple procedures. The first is designed to exclude Ad-

dison's disease as the cause of fatigue, hypotension and neurasthenic symptoms simulating Addison's disease. It can be completed within 18 hours and does not require any chemical determinations. The test is conducted by comparing the volume of urine excreted during a nocturnal period of dehydration with the volume of urine excreted after the ingestion of water. Normal diuresis excludes Addison's disease. Delayed excretion of water is suggestive, but not diagnostic, of this condition.

The second procedure involves analysis of the plasma and nocturnal urine for urea and chlorides. From these data the following ratio is calculated:

$$A = \frac{\text{Urea in urine (mg.\%)}}{\text{Urea in plasma (mg.\%)}} \times \frac{\text{Chloride in plasma (mg.\%)}}{\text{Chloride in urine (mg.\%)}} \times \frac{\text{Volume of day urine (cc.)}}{\text{Volume of night urine (cc.)}}$$

If the value for the ratio is less than 25, the patient probably has Addison's disease. False positive results may occur in certain conditions such as nephritis. On the whole, this procedure compares favorably with the more complicated diagnostic procedures which require deprivation of salt or measured response to specific therapy. An analysis of the results obtained in almost 100 cases, in about half of which the diagnosis of Addison's disease was proved, will be presented.

60. Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-leydigism, and Increased Excretion of Follicle-Stimulating-Hormone

Harry F. Klinefelter, Jr., Edward C. Reifenstein, Jr. and Fuller Albright, *Massachusetts General Hospital, Boston*

The authors have studied ten cases of a fairly common syndrome which has not received much attention in the literature. It is characterized by small testes with aspermatogenesis, bilateral gynecomastia, marked increase in urinary FSH excretion, only moderate reduction in urinary 17-ketosteroid excretion, and only slight reduction in Leydig cell function.

Biopsies of the testes show practically complete absence of tubular elements with preservation of the interstitial cells. The breast tissue shows proliferation of duct epithelium and of the periductal connective tissue.

This report includes discussion of *a*), therapeutic effects of testosterone and estradiol, *b*), pathogenesis, and *c*), the bearing of these findings on the physiology of the testis.

50. Effect of Testosterone Propionate and Castration on the Alkaline and Acid Phosphatases of the Kidney, Liver and Small Intestine

Charles D. Kochakian and R. Phyllis Fox *University of Rochester, Rochester*

The alkaline and acid phosphatases of the kidney, liver and small intestine of normal and castrate male mice with and without testosterone propionate treatment were determined. Also the alkaline phosphatase of the kidneys of normal and normal plus testosterone propionate-treated female mice was determined. The androgen was implanted subcutaneously as a pellet of about 20 mg. when the animals were approximately 5 weeks old. The phosphatase determinations were made one month later. The alkaline phosphatase in the kidneys of both the treated males and females was only slightly greater than that of the normals on a total basis but much less on a per gram basis. The decrease was due to the hypertrophy of the kidneys as a result of androgen therapy. On the other hand, the acid phosphatase of the kidney increased in almost direct proportion to the increase in kidney weight. The alkaline phosphatase of the liver decreased as a result of castration but increased under therapy. The acid phosphatase of the liver showed no notable changes. The acid and alkaline phosphatases of the small intestine were not affected by either castration or androgen therapy.

20. Kidney Function and Blood Chemical changes in Hyperparathyroidism

G. F. Koepf, Crichton MacNiel, Nils Klendshoj and N. G. Russell. *Department of Medicine, University of Buffalo School of Medicine, and the Metabolic Division of the Buffalo General Hospital, Buffalo*

Metabolic studies were carried out on a patient with an adenoma of the parathyroid gland (characterized clinically by an exceptionally acute onset) before and after removal of the tumor. Changes in the serum levels of calcium, phosphorus and phosphatase are correlated with alterations, in renal function and bony structure. The following changes were noted. 1). The serum calcium level dropped to normal within 48 hours after operation, but the serum phosphorus remained low for several weeks before rising to normal. 2). The acid and alkaline phosphatase activities of the serum were both elevated prior to removal of the tumor. An even greater elevation of these values was noted during the first two postoperative weeks. A gradual regression to normal then took place. 3). The changes in renal function in this instance were alleviated by removal of the tumor. 4). There was a steady recalcification of the cystic areas in the bones after removal of the tumor. These studies

indicate that the serum phosphatase activity may be a measure of osteoblastic activity. Early renal damage in hyperparathyroidism may be reversible.

17. Adrenal Cortical Hormonal Requirements of Adrenalectomized Rats Exposed to Low Atmospheric Pressure

L. L. Langley. *Laboratory of Physiology, Yale University School of Medicine, New Haven*

The work of Giragossintz and Sundstroem (*Proc. Soc. Exper. Biol.*, 1937, 36: 432), has been repeated and extended. Using the normal weight curves as criteria of maintenance, 0.03 mg./day of desoxycorticosterone acetate, or 0.5 cc./day of adrenal cortical extract (Wilson) have been found to be adequate to maintain 200 gm.-adrenalectomized rats at sea-level. If the animals are injected with this dosage while exposed to 20,000 feet altitude, there is a progressive loss of weight, and death invariably occurs without any detectable adjustment being made to this environment. However, at this pressure the animal may be maintained in good condition using 3 cc./day of the extract, or 1 mg./day of desoxycorticosterone acetate.

Using this high dosage the weight curve is indistinguishable from that of a normal animal exposed to anoxia. There is a marked loss of weight during the first 2 or 3 days, after which a slow, but progressive gain occurs. At this point, i.e., after exposure to low atmospheric pressure for about 6 days, the dosage may be reduced to maintenance sea-level values, and the animal will continue to survive in good health, and to gain in body weight.

It is concluded, therefore, that an increase in adrenal cortical activity is required during the process of acclimatization to low atmospheric pressure, after which the output of the adrenal cortex returns to normal, at 20,000 ft. in the rat.

24. Treatment of Acne with Orally Administered Estrogens

Charles H. Lawrence and Nicholas T Werthessen. *Department of Medicine, Tufts College Medical School and The Endocrine Clinic and Laboratory of the Boston Dispensary, Boston*

The authors have previously shown that in females with acne there is a disturbance of androgen-estrogen balance, resulting in insufficient estrogens to protect the individual against the known acnegenic effect of androgens. The present paper presents the results of treatment of 25 acne patients with stilbestrol and ethinyl estradiol: 11 males and 14 females were treated, with marked benefit in every patient. The age factor, diet factor, menstrual exacerbations, effect of pregnancy, and incidence of coincidental menstrual disturbances in the patients are discussed. The rationale of the treatment and details of dosage and administration are discussed in detail, and contraindications and by-effects are considered. The authors conclude that the treatment is, on the basis of their previous study, logical, highly effective, and, under proper control, safe.

35. Purification of Pregnant Mare Serum and its Effect on the Appearance of Antigonadotropic Substances in Human Sera

J. H. Leathem and A. R. Abarbanel. *Department of Zoology, Rutgers University, New Brunswick and the Department of Anatomy, College of Physicians and Surgeons, Columbia University and Harlem Hospital, New York City*

Women suffering from amenorrhea were treated with either of 2 preparations of pregnant mare serum, one being 2½ times more highly purified than the other. Patients generally received 4 injections of PMS, 'gonadogen,' during 9 to 12 days of each month's treatment and total dosages of 40 to 450 R.U. were administered during periods of 1 to 3 months.

Immature mice or rats were used to test the antigonadotropic activity of the sera. The animals received a total of 0.5 R.U. of PMS and, at a different site, 0.9 cc. of serum. Injections were made subcutaneously once daily for 3 days and the animals sacrificed 72 hours after the first injection. The sera were tested prior to hormone administration and at varied intervals up to 41 weeks after the initial injection, 10 samples being the maximum number studied from one patient.

Prior to hormone treatment, serum of only one of 39 patients exhibited inhibitory activity. Six of 7 patients injected with less purified preparation developed antigonadotropic substances in their blood, generally first evident in 9 to 10 weeks after the initial injection. Twelve patients were treated with the more highly purified and in only one individual was an antigonadotropic serum developed.

5. Hormone Action of Thyroglobulin Antibodies

Jacob Lerman. *Boston*

The specific protein of the thyroid (thyroglobulin) is strongly antigenic.

The antibodies to thyroglobulin are not 'species-specific' but rather 'hormone-specific.' They will neutralize the thyroglobulins of all related species, including the one from the donor animals. For example, antiserum made by injecting rabbits with human thyroglobulin will agglutinate not only all mammalian thyroglobulins but also rabbit thyroglobulin.

Animals immunized with thyroglobulin fail to show the expected metabolic rise and weight

loss with subsequent injections, i.e. they are 'refractory.' In other words the antibodies inhibit the physiologic action of thyroid protein.

Animals (8 of 9 rabbits) immunized with thyroglobulin over a period of 6 months or more develop myxedema. It indicates clearly that the antibodies of these animals inhibit in some way the secretion of thyroid hormone or its physiologic activity.

These facts suggest that the antiserum treatment of Graves' disease, long ago attempted but crudely executed, should be re-evaluated.

15. Carbohydrate Metabolism of Methyltestosterone-Treated Patients

Lena A. Lewis and E. P. McCullagh. *The Cleveland Clinic, Cleveland*

Treatment of patients with large doses of methyl testosterone for long periods results in a modification of glucose tolerance. Studies have been extended to determine the factors involved in producing this change. Glucose tolerance, basal metabolic rate, and hepatic glycogen stores, using the phlorhizin technic of Mirsky, have been studied at various times in the course of treatment. A decreased glucose tolerance was observed following treatment for a period of weeks with large doses (80 to 200 mg. per day) of methyl testosterone. Basal metabolic rates were not increased in all cases. Where the basal metabolic rate was increased, there was a decrease in sugar tolerance. A decrease in liver glycogen stores usually accompanied the modified glucose tolerance. In some of the methyl testosterone cases, the total glucose excreted was as great following phlorhizin injections as in the control test, but a significant part was from the body fluids, as indicated by the decreased blood sugar at the end of the test. The decreased glucose excretion observed in some cases, therefore, cannot be explained by modification of the kidney tubules.

In some cases by increasing the carbohydrate intake, the modified sugar tolerance was brought to normal limits. Despite continued hormone administration, high carbohydrate feeding restored liver glycogen to levels observed when no medication was being given. This effect on sugar tolerance is similar to that observed in some cases of hyperthyroidism.

3. Experimental Hypothalamic Obesity in the Rat

C. N. H. Long, John R. Brobeck and Jay Tepperman. *Department of Physiological Chemistry, Yale University School of Medicine, New Haven*

Bilateral, symmetrical electrolytic lesions were placed in the hypothalami of rats by means of the Horsley-Clarke stereotaxic instrument. Almost immediately after operation the animals began to eat voraciously, often consuming 2 to 3 times the amount of food eaten by their littermate controls; and they became very obese. Ten operated rats pair-fed with their controls frequently ate their day's ration in less than 2 hours, but (with one exception) none outgained its control. The development of the obesity is apparently a consequence of the increased appetite and is not associated with any fundamental disturbance in metabolism. The basal oxygen consumption of pair-fed operated rats was normal. The absolute oxygen consumption of fat rats fed *ad libitum*, however, was occasionally as much as twice that of their controls.

The fasting R.Q.'s of both fat and pair-fed operated animals were similar to those of normal rats, but the R.Q.'s after glucose of all operated rats were abnormally high. Normal animals trained to eat their daily ration in 3 hours or less showed R.Q.'s in the same range as those observed in the operated animals.

Albuminuria (often associated with casts) was observed in 13 of 15 operated rats from 8 to 12 weeks after they became obese, and 4 of these showed striking histological changes in the glomeruli and tubules. Littermate controls and pair-fed operated rats showed no evidence of renal damage.

19. A Thyroid-Adrenal Relation in Resistance to Potassium

B. E. Lowenstein and R. L. Zwemer. *Department of Anatomy, College of Physicians and Surgeons Columbia University, New York*

In rats given daily injections of desoxycorticosterone acetate in oil, the adrenal cortex undergoes changes (depending on the dose) from slight lipoid depletion to physiological atrophy. On the other hand, rats fed small amounts of desiccated thyroid daily showed adrenal cortex hypertrophy, but with increasing doses of thyroid there was adrenal cortex depletion. The relation of the morphology of the glands to physiologic resistance of the animal was tested by potassium injection. Rats given a carefully adjusted dosage of both thyroid and desoxycorticosterone acetate can be maintained at approximately the same resistance to potassium as the controls. This balancing effect cannot be obtained with high dosages.

61. Intraosseus Injections of some Endocrine Compounds

David I. Macht and Elizabeth C. Spencer. *Pharmacological Research Laboratory, Hynson, Westcott & Dunning, Inc., Baltimore*

The pharmacodynamics of oils, fixed or volatile, may be conveniently studied by intramedullar injection into long bones. Such common fixed oils as olive, sesame, peach kernel, peanut and mineral

oils injected in small doses into tibia, femur or humerus of various animals, are not toxic and rarely cause embolism. Active principles dissolved therein, when introduced into bone marrow, are slowly released and exert characteristic physiological effects. Three endocrines have been thus studied by the authors. Estradiol in olive or peanut oil, injected into tibias of spayed rats and guinea pigs, produced positive vaginal smears. Crystalline progesterone, dissolved in sesame oil, injected into tibias of Clauberg rabbits, caused typical progestational proliferation of endometrium. Oily suspensions of epinephrine, injected *intramuscularly* in cats, caused little rise in blood pressure. Aqueous adrenalin injected into the bone marrow is absorbed as rapidly as when given by vein, producing an immediate rise in blood pressure, which promptly returns to normal level. Epinephrine in *oil*, however, on intraosseus injection effects a marked rise in blood pressure which lasts from 15 to 45 minutes.

16. Study of the Relative Effectiveness of Different Modes of Administration of Insulin

E. P. McCullagh and Lena A. Lewis. *The Cleveland Clinic, Cleveland*

The effective use of pellet implants of different hormone preparations suggested an investigation of this mode of administering insulin. Normal adult dogs maintained on a constant diet were used. Their normal fasting blood sugar values were determined after which varying doses of regular (amorphous) insulin were given, and the blood sugar values repeatedly determined. The effect of daily doses of protamine zinc insulin was also studied. Silver capsules (2 mm. diameter ×100 mm. open at the ends) were firmly packed with crystalline zinc insulin and implanted subcutaneously. As indicated by the decrease in the fasting blood sugar levels, the rate of release of insulin was fairly constant for the first few days. The release gradually decreased until after 2 or 3 weeks no effect was observed. After 3 or 4 weeks the capsules were removed and found to contain appreciable amounts of potent insulin. Examination of the tissue surrounding the capsule showed a mass of granulation tissue typical of that forming around a non-irritating foreign body. In one case no release of insulin was detectable 2 days after implantation. On removal of the capsule, a firm fibrin-like clot was found in the open ends of the tube.

Pellets were prepared by firmly packing thoroughly mixed 20% crystalline insulin and 80% cholesterol into a mold. Preliminary experiments using crystalline albumin-cholesterol mixtures indicated that a 20% insulin mixture would release about 1 mg. of insulin per day. Following the implantation the blood sugar level dropped to approximately that which followed administration of 25 to 30 U of protamine insulin. As occurred with the use of the silver capsules, the absorption decreased until no appreciable release was observed after about 3 weeks. The pellets after several weeks became somewhat 'mushy' but were prevented from disintegrating by the tissue capsule around them. In some cases after the initial pellet had been implanted for 3 or 4 weeks, a second pellet was inserted. A response very similar to that following the first implantation was observed.

52. Experimental Modification of Water and Salt Output in Patients With Diabetes Insipidus

Thomas H. McGavack, H. Elias and P. Gelvin. *New York Medical College, New York City*

Three patients with the syndrome of diabetes insipidus are the subjects of the study. In each patient studies were made of the comparative influence of water deprivation, low and high salt intake, amidopyrine, estrogenic hormone, desoxycorticosterone acetate, and various posterior pituitary preparations upon the urinary volume and output of sodium and chlorides.

12. Species Difference in Diabetes Mellitus

I. Arthur Mirsky, Norton Nelson and Samuel Elgart. *The May Institute for Medical Research, The Jewish Hospital, Cincinnati*

It has been known for some time that the removal of the pancreas does not result in the development of the same syndrome in all species. Nevertheless, very few systematic studies have been performed with regard to this problem. In this study the diabetic syndromes of man, monkey, cat, dog, duck, owl, goat, pig, rabbit, and rat are compared and the mechanisms responsible for the differences are discussed.

46. The 17-Keto Steroid Complex in Normal Men's Urine

Paul L. Munson, T. F. Gallagher and F. C. Koch. *Department of Biochemistry, University of Chicago, Chicago*

The extraction, purification and hydrolysis of conjugated 17-ketosteroids of men's urine will be discussed. During the coarse fractionation of conjugated forms of urinary 17-ketosteroids, treatment of a purified extract with semi-carbazide yielded a white amorphous powder which is apparently principally semi-carbazone of a 17-ketosteroid sodium sul-phate.

37. Gonadotropic Factors Influencing the Function of the Corpus Luteum

Warren O. Nelson and Eugene Cutuly. *Wayne University College of Medicine, Detroit*

Studies have been made on hypophysectomized female rats which had been treated with follicle-stimulating and luteinizing factors alone and in combination. Although combined treatment resulted in the growth of follicles and the production of numerous corpora lutea, there was evidence of estrogenic effects only. Vaginal smears, vaginal and uterine sections, and mammary gland mounts and sections showed effects similar to those seen with follicle-stimulating hormone only. The addition of lactogenic hormone to the combined treatment resulted in evidence of progestin activity in vaginae, uteri and mammary glands. Presumably, the preparations of lactogenic hormone contained the so-called luteotropic factor, or the lactogenic and luteotropic factors are identical. It is supposed that the luteotropic principle is responsible for functional activity of the corpus luteum.

In examining these possibilities a series of pituitary fractions have been examined for luteotropic activity. Crude extracts, partially purified fractions containing appreciable quantities of both adrenotropic and lactogenic factors, and relatively pure fractions of adrenotropic and of lactogenic factors have been used in this phase of the study. It has been apparent that the activity in terms of the luteotropic factor follows reasonably closely the content of lactogenic hormone in preparations which have been studied.

45. A New Color Reaction of Androsterone and Related Compounds

Gregory Pincus. *The Physiological Laboratories, Clark University, Worcester*

Androsterone, its isomers, etiocholanol-3α-17 one and etioallocholanol-3β-17 one, and androstenone-17 react to give an intense blue color (absorption maximum 620-630$\mu\mu$) after heating with a concentrated solution of $SbCl_3$ in glacial acetic acid and dilution with acetic acid (or acetic anhydride). A similar but less intense color is given by androstanediol. A number of other neutral steroids do not give this color reaction. Those tested are: testosterone, dehydroisoandrosterone, androstanol-3β-1 one, epipregnanolone, allopregnanololone, desoxycorticosterone, progesterone, pregnandiol, cholesterol, and cholestenone. The reaction may be applied to various neutral urinary extracts. The results indicate that the Zimmerman color titer of such extracts may, in certain types of urine especially, give a gross overestimate if it is taken as 'androsterone equivalent.' The utility of the reaction as a more specific measure of urinary androgen will be demonstrated.

49. Effects of Testosterone on Hypogonadism

J. P. Pratt, *Henry Ford Hospital, Detroit*

An adult eunuchoid physician who prefers to remain anonymous has permitted his own case report to be presented. He compares the effects of gonadotropic pituitary, pituitary-like preparations, testosterone propionate and methyl testosterone. Conspicuous physical and psychologic changes were induced by testosterone but all other preparations were ineffective. Physical effects noted were pigmentation of the skin, especially on the genitalia and nipples; development of coarse black curly hair on the pubis; growth of the beard; a threefold increase in the size of the penis; development of the epididymides and prostate; seminal fluid devoid of spermatozoa increased to 2.5 cc.; the larynx became prominent and the voice lower; sebaceous glands were more active, and erection, even priapism, were noted.

The most striking and gratifying changes were psychologic. Periods of depression, formerly frequent, disappeared. His general spirits were greatly improved. Shyness was replaced by aggressiveness, at times even pugnacity. Friends remarked that he seemed "more mature," "emotionally more stable." The desire for feminine companionship increased. Libido appeared and increased. Development of tolerance was noted. Dosage levels were compared.

43. Measurement of an Alpha, Beta, Unsaturated Ketosteroid (Progesterone) Obtained from Serum: Microanalysis by a Spectophotometric Method

Samuel R. M. Reynolds. *Department of Embryology, Carnegie Institution of Washington, Baltimore*

The Corner-Allen method of assaying progestational activity led to the identification of the corpus luteum hormone, progesterone. The method has proven of great value, but it is limited by the fact that a minimal, positive test requires about 1 mg. of material, and 2 or more rabbits are necessary for quantitative examination of material from unknown sources. An efficient method of quantification is desired for the detection of very small amounts of progesterone. With certain limitations, this has been achieved by means of ultraviolet absorption spectrophotometry, using a Hilger medium quartz spectograph and a logarithmic sector. Data published in the literature on absorption of a variety of steroids and related substances have been confirmed. Extinction-concentration curves have been established and the limits of sensitivity of the test thus ascertained. Since the method employed for extracting progesterone from serum does not separate it from estrogens, absorption-concentration curves for the latter have

been established. By measuring absorption due to estrogens at one part of the spectrum (265–280 μμ), a correction factor may be applied in the region of greater absorption resulting from progesterone (240–250 μμ). The hormones have been added separately, as well as together, in varying concentrations to 10 cc. portions of serum from castrated rabbits. Preliminary tests have shown that, under good conditions of extraction, 5 μg. per cc. can be detected with an error of about 15% or less.

The test must be restricted for the present to experimental conditions in which it is certain, or highly probable, that progesterone is involved. This is necessary since distinction cannot be made, in unknown materials, between such substances as progesterone, testosterone, desoxycorticosterone and androstendione.

26. Effects of Estrogenic Substances Upon the Buccal Mucous Membrane

M. J. Richman and A. R. Abarbanel. *Departments of Dentistry and Gynecology, Harlem Hospital, New York City*

The effects of estrogens upon the buccal mucous membrane of fifty menopausal patients were studied. Before therapy, many of these patients complained of a peculiar dry or burning sensation in their mouth. After suitable estrogenic therapy, the oral symptoms were relieved. Biopsies of the buccal mucosa, and in several instances of the vagina, before, during and after estrogen administration (estradiol or stilbestrol) were made. In every case where an atrophic buccal mucosa was found, the epithelium responded to estrogen in exactly the same manner as did the vaginal mucosa. When the estrogen was injected directly under the buccal mucosa, the response was more rapid and greater, dose for dose, in comparison to the intramuscular route. Histologically, the prickle cell layer showed a marked growth increase. The corneous layer was also increased in thickness and keratinization. The rete papillae became extremely vascular. In summary, then, estrogens are capable of restoring the atrophic buccal mucous membrane of the human female to a normal status.

13. Carbohydrate, Fat, and Protein Appetite of Pancreatectomized Rats

Curt P. Richter and E. C. H. Schmidt, Jr. *Psychobiological Laboratory, Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore*

In the present experiment, rats in individual self-selection cages were permitted to select their own diet for 40 days preoperatively and 40 days postoperatively from the following 15 purified substances: dextrose, casein (purified), olive oil, aqueous solutions of sodium chloride, sodium phosphate, calcium lactate, potassium chloride, magnesium chloride, thiamine chloride, riboflavin, nicotinic acid, pyrodoxin, pantothenic acid, choline chloride, and cod liver oil. During the preoperative period the rats grew at a fairly normal rate or at least maintained their starting weight. They showed regular 4–5 day estrous cycles and did not show any signs of deficiency.

After they had been on the diet for 40 days, they were partially pancreatectomized, small fragments of pancreatic tissue being left between the bile duct and the duodenum. After pancreatectomy they showed a markedly increased appetite for olive oil and casein and a decreased appetite for dextrose. They also showed an increased appetite for the crystalline members of the vitamin B complex, except possibly for thiamine. By virtue of their selections they maintained their weight and showed only slight if any polyphagia or polydipsia. Later, when placed on the stock diet nearly all of the animals manifested the typical symptoms of diabetes.

Full replacement could be obtained with a mixture which had a high fat, high protein, and high vitamin B complex content, and a very low carbohydrate content. Of the different components of the vitamin B complex riboflavin appeared to play the most important rôle.

63. Combined Use of Testosterone Propionate and Psychotherapy in the Treatment of Hypogonadal Behavior-Problem Boys

H. S. Rubinstein. *Laboratory for Neuroendocrine Research, Surgical Division, Sinai Hospital, Baltimore*

This study emphasizes the psychosomatic aspects frequently observed in the endocrinopathic child and the advantage of a therapy which considers the personality as a whole. Maladaptation in a group of 15 boys referred for study and treatment because of behavior difficulties was directly traced to either a frank or masked hypogonadism. Treatment with the testosterone propionate usually commencing with 25 mg. 2 or 3 times weekly, led to phallic growth in all cases. In several patients with undescended testes, testicular descent and growth also resulted. Concomitant psychotherapy was also carried on. All 15 patients responded by establishing more satisfactory attitudes toward their defects and all developed more acceptable forms of behavior. Other dysplastically constituted behavior-problem children, however, failed to improve in their behavior in spite of continued psychotherapy after the correction of their physical defects.

40. Effects of Insulin, Thyroxin and their Combination on the Metabolism of the Brown-Pearce Epithelioma and its Host

Robert Ryer, III and J. R. Murlin. *Department of Vital Economics, University of Rochester, Rochester*

Previous reports have shown that these hormones administered singly or in combination to the host (rabbit) restrict sharply the tumor metastases. This report deals with effects by these hormones singly and in combination on the energy metabolism of the entire animal and the metabolism of tumor and liver tissues of the host. Regular insulin (½U. per kg. of body weight) evokes an increase of 20% in total metabolism during the 3rd and 4th hours after administration. Tumor and liver tissues respond with a 70% increase of oxygen uptake when removed at the point of convulsions. Thyroxin (½ mg. per kg. once a week) causes an average increase of total metabolism over that period of 45%. Tumor tissue taken on successive days post thyroxin shows an average increase in O_2 uptake of 80% over tumor from non-thyroxinized animals. Liver tissue shows an increase of only 53%. Insulin superimposed the first 3 days after thyroxin elicits a 100% increase in O_2 consumption of liver tissue and 180% increase in O_2 consumption of tumor tissue. Correlations with gross effects on the tumor are presented.

48. Effect of Androgens upon Libido in Women

Udall J. Salmon and Samuel H. Geist. *Mt. Sinai Hospital, New York City*

During the course of therapeutic administration of testosterone propionate for dysmenorrhea, meno-metrorrhagia and premenstrual tension, the observation was made that libido was apparently increased in a number of the women. A series of studies were consequently undertaken to determine whether or not androgens have a specific effect upon the psychosexual mechanism. The study was made on a group of women with apparently normal psychosexual reactions and a group with diminished or absent libido. The latter group consisted of: *a*), women who had had normal psychosexual reactions, but in whom there had occurred, as a result of an endocrine disorder (e.g. secondary amenorrhea, natural menopause, and x-ray or surgical castration), a complete loss of sexual desire and the ability to have an orgasm; and *b*), a group of women who complained of frigidity but who presented no evidence of an endocrine disorder. Patients in whom psychogenic factors appeared to play an etiologic role were excluded from the study.

The effects of the following hormones were studied: testosterone propionate (intramuscular), methyl testosterone (oral) and testosterone in propylene glycol (sublingual). Subsequently estrogens were substituted for the androgens without the patients' knowledge. The androgens had the following effects: *a*), they caused a heightened susceptibility to psychic and physical sexual stimulation; *b*), produced an increased sensitivity of the external genitalia; and, *c*), induced a greater intensity of sexual gratification.

The effects in the majority of instances gradually disappeared within six weeks after discontinuation of the androgens. Administration of estrogens to these patients, subsequently, produced none of these stimulative effects.

68. (Motion Picture). A Rapid Pregnancy Test (2 to 6 Hours)

U. J. Salmon, S. H. Geist, I. L. Frank, C. Poole and A. A. Salmon. *The Mount Sinai Hospital, New York City*

Earlier studies have demonstrated that the administration of human pregnancy urine to immature female rats causes marked hyperemia of the ovaries, which is grossly visible 6 hours after the injection. This was utilized as a test for human pregnancy.

The vaso-dilating effects of the pregnancy urine were studied at hourly intervals for a total of 6 hours. The ovarian hyperemia was detectable grossly as early as 2 hours after the injection of the pregnancy urine.

It is suggested that in clinical conditions in which it is important to determine the presence or absence of pregnancy, that a reading can be obtained in 2 hours, and in doubtful cases, the report checked by the 4 and 6 hours readings.

The film demonstrates the gross appearance of the ovaries at 2, 4 and 6 hours in "positive" animals and "negative" controls; microphotographs of sections of the ovaries are included showing the vascular dilatation in contrast to the "negative" controls.

64. Physiological Method for Measuring Adrenal Steroid Activity

J. P. Schooley. *Difco Laboratories Incorporated, Detroit*

During experiments with rats in which the ovarian follicular apparatus and the adrenal cortex had been damaged or destroyed by x-ray, it was noted that if the animals were given a choice between 0.9% saline and tap water, the increased fluid intake was in the direction of increased use of salt water with the intake of tap water remaining relatively constant. Other groups of animals were prepared and accurate measurements were

undertaken to determine the validity of this primary observation. It was found that the state of adrenal steroid production, or administration, can be analyzed objectively by measuring the differential intake of salt and tap water in adrenalectomized or x-ray-treated rats.

67. Role of the Liver in the Metabolism of Estrogens

Albert Segaloff and Warren O. Nelson. *Wayne University, College of Medicine, Detroit*

In evaluating the role of the liver in metabolizing estrogens, intrasplenic injections were made of α-estradiol, estrone, certain esters of these, and of estriol. Controls were injected subcutaneously. In one group of rats injections were made intrasplenically with spleens *in situ*. In a second group of rats injections were made into spleens which had been transplanted subcutaneously.

Although α-estradiol-3-benzoate was more effective, in terms of mg. equivalents, than free α-estradiol when injections were made intrasplenically in animals with spleens *in situ*, the ratio of effectiveness in animals with transplanted and with non-transplanted spleens was the same for the two compounds. This same comparison holds true for estrone and estrone-3-benzoate. However, a comparison of α-estradiol dipropionate and α-estradiol-3-benzoate-17-butyrate with free α-estradiol showed that these diesters are more potent than free α-estradiol both absolutely and on the basis of ratios, the dipropionate being 3 times, and the benzoate butyrate 25 times, as effective as free hormone. The results indicate that the liver attacks α-estradiol at its hydroxyl groups and that the 17-hydroxyl is probably the more important hydroxyl group. The ketone group of estrone is probably the prime site of inactivation by the liver. The results also indicate that at least the diesters of estradiol are absorbed from the spleen as such since they show increased effectiveness over the free hormone when injected into the spleen *in situ*.

31. Fundamental Rules Regulating the Actions of Steroid Hormones

Hans Selye. *Department of Anatomy, McGill University, Montreal*

On the basis of experiments in the rat 7 main activities of the steroid hormones could be characterized as independent of each other: the corticoid (cortical hormone-like), luteoid (corpus luteum hormone-like), testoid (testis hormone-like) folliculoid (estrogenic), pro-renal (renotropic), spermatogenic and anesthetic properties. These differ fundamentally from the so-called 'subordinate actions' which are merely partial manifestations of an independent pharmacological property. The independent nature of an effect has been proven by comparative bioassays showing that the degree to which it manifests itself in a series of hormonally active steroids does not run parallel with any other independent action. The subordinate nature of an effect is demonstrated by the existence of a close parallelism between it and all other manifestations of the independent group to which it belongs.

A distinction is made between manifest (or overt) and masked hormone actions. Thus the vagina-cornifying effect of estradiol is manifest, while that of testosterone is masked although it may become overt after hypophysectomy. On a large series of steroids it has been shown that the folliculoid and anesthetic properties are detectable in all hormonally active compounds although in some they are normally present in a masked form.

21. An Evaluation of the Pregnandiol Complex as Determined by the Venning-Brown Test

Samuel L. Siegler and David W. Bauer. *Unity Hospital, Brooklyn*

We have attempted to evaluate pregnandiol excretion as a diagnostic aid in the determination of the presence or absence of ovarian function. For this purpose, titration studies of sodium pregnandiol glucuronidate were undertaken on the urine of women with normal menstrual cycles, those with abnormal menstrual cycles, before and following hormone therapy, and those upon whom panhysterectomy, hysterectomy and bilateral oophorectomy had been performed. Endometrial biopsy studies were concurrently done, in an attempt to to correlate our findings.

Sodium oregnandiol glucoronidate excretion per se, is not a reliable index of ovulation. The endometrium is not absolutely necessary for the metabolism of progesterone.

65. Relationship in Clinical Results of Para-aminobenzoic Acid and Certain Hormones

Benjamin E. Sieve, *Boston City Hospital and Tufts College Medical School, Boston*

Human achromotrichia has attracted wide attention as to its etiology. When para-aminobenzoic acid was proven to be a vitamin playing a role in enzymic pigmentation processes it soon became evident that para-aminobenzoic acid had some metabolic effect on areas of pigmentation on the human body other than hair. Data on these observations are presented, together with further clinical results of treatment with para-aminobenzoic acid and hormones on libido, amenorrhea, and female sterility. An hypothesis is entertained that para-aminobenzoic acid may be either considered a hormone itself or possibly a catalyst or enzyme activating a hormone.

18. Reaction of Orbital Tissues in Experimental Exophthalmos Following Removal of Harder's Gland

George K. Smelser. *College of Physicians and Surgeons of Columbia University, New York City*

Exophthalmos following injection of anterior pituitary extracts into thyroidectomized guinea-pigs is due to hypertrophied retrobulbar tissues. Since Harder's gland (absent in the human) contributed considerably to this protrusion, it seemed advisable to determine the effect of pituitary extracts on the orbital fat and muscles, and on the protrusion of the eye, in the absence of this gland. Exophthalmos was produced in guinea-pigs in which the Harderian gland had been removed from one orbit. In the first series orbital fat was grafted into the orbit, partially correcting the marked sinking of the globe following extirpation of the gland. In a second series the gland was replaced by fat from the ovario-uterine mesentery. In a third group Harder's gland was removed at birth with no attempt at replacement. A definite proptosis was observed in all 3 groups in the absence of the Harderian gland as well as on the unoperated side. The exophthalmos produced was accompanied by hypertrophy (40%) and pathological modification of the orbital fat and muscles. The edematous infiltration was comparable to that described in clinical and experimental post-thyroidectomy exophthalmos and indicates that these changes as well as the proptosis are not dependent upon the presence of Harder's gland.

23. Relationship Between Estrogenic Hormones, Extracellular Fluids and Resistance to Viral Infections

Douglas H. Sprunt and Heywood Taylor. *Department of Pathology and Biochemistry of Duke University Medical School, Durham*

Rabbits receiving estrogenic hormones are known to be more resistant to dermal infection with vaccinia virus. Rabbits which had received estrogenic hormones for 3 weeks were shown to have a statistically significant increase in total blood volume and available extracellular water. These animals were also found by direct studies of the skin to have a significant increase in available extracellular fluid in the skin. In other experiments in which the amount of available extracellular fluid was increased by other methods there was also a decrease in the rabbit's susceptibility to infection with vaccinia virus.

It is thought that the decrease in susceptibility brought on by an increase in extracellular fluids is due to the fact that when the available extracellular fluid is increased the spread of the virus in the skin is decreased. This limitation of spread leads to fewer susceptible cells being exposed to the virus and hence a decreased likelihood of infection occurring. It is, however, possible that the increased resistance is the result of a change in cell permeability resulting from the change in water balance.

28A. Changes in the Peripheral Blood and Bone Marrow of Rats Treated with a New Synthetic Estrogen

Robert B. Stebbins and Ernest W. Blanchard. *Research Laboratories, Schieffelin & Company, New York City*

The synthetic estrogen, 2,4 di(parahydroxphenyl)-3-ethyl hexane, '-118B-' was administered to groups of castrate and normal rats, in amounts ranging from minimal estrus doses to those 1000 times the effective level by 3 routes: subcutaneously in oil; orally in 40% ethyl alcohol; and by implantation in the form of pellets. Similar administrations of natural estrogen served as controls, and in certain instances, like amounts of diethyl stilbestrol were given for comparison. Blood samples were drawn at frequent intervals throughout the experiments.

A decrease, of varying degree, in erythrocyte count and percentage of hemoglobin followed these extended administrations. This tended to be an initial drop followed by stabilization at a lower value. The decreases were appreciably less in the rats receiving the material orally, and a marked tendency to return to the normal level during treatment was noted. The animals receiving natural estrogen and stilbestrol did not show this tendency. Rats implanted with 20–250 mg. pellets of 118B showed appreciable drops in erythrocyte count and per cent hemoglobin, which changes were completely reversible following removal of the pellets. Reticulocyte counts were done in all instances but the changes were very slight.

In those animals where bone marrow changes were observed, they were first reflected by an increase in cellularity of the myeloid elements, followed by a general hypoplasia. This marrow depression was completely repaired upon cessation of treatment. (*See also abstract 28, Blanchard, E. W.*)

62. Non-Neoplastic Hypergenitalism

Nelson Taylor and Robert L. Schaefer. *Wayne County Clinic for Child Study, Detroit*

Seventeen cases of hypergenitalism are analyzed with respect to physical, psychological and social findings. A composite description of this endocrine type is then presented. The most remarkable physical characteristics are relatively short 'long bones,' excessive musculature, very good teeth, hyperplastic male genitalia or female mammae. Premature epiphyseal closure is usually noted. School progress and adjustment are usually

poor and recreational interests are passive with a scarcity of intimate companions. There will probably be some abnormal habit and if delinquency occurs it will probably be sexual in nature.

Retardation in general intelligence is to be expected but manipulative ability may be average or above. Emotional instability, immaturity and suggestibility are the rule. Poor planning capacity and defective social judgment may be expected. Autocriticism will likely be lacking and there probably will be little self-confidence. The patient may be impulsive, uninhibited or display temper tantrums. There may be abnormal apprehension and marked traits of dependence.

No treatment is suggested but understanding of the problem is essential for all who manage children and adolescents.

29. Experiences with a New Synthetic Estrogen for Oral Administration

S. G. Taylor, III, and W. O. Thompson. *University of Chicago, Chicago*

Observations have been made on the effect of oral administration of a new synthetic estrogen closely related to stilbestrol. (Schieffelin Product 118B). An attempt has been made to compare its estrogenic potency with that of other estrogenic substances of known potency by means of vaginal smear studies and subjective control of the symptoms of the menopause. Although it has been reported to be about ⅓ as effective as stilbestrol by mouth, it has been necessary in our hands to administer from 30 to 50 mg. by mouth daily to produce the same estrogenic effect as with 1 mg. of stilbestrol. Nausea, vomiting, heartburn, and leg cramps have been much less frequent during the administration of this drug than with stilbestrol, but have been noted in some instances.

51. Endocrine Regulation of Growth

W. O. Thompson, Norris J. Heckel and R. P. Morris. *University of Chicago, Chicago*

The pituitary growth factor appears to be responsible for growth in length whereas the gonadotropic factor appears to be responsible primarily for skeletal moulding, but also for some growth in length. The growth factor produces gigantism before epiphyseal closure and acromegaly after the epiphyses are closed. The action of the thyroid hormone is different in that in therapeutic doses it does not stimulate the growth of normal children, and large doses do not alter the final height of the skeleton. The influence of the gonadotropic factor on growth appears to be correlated with the growth that occurs normally at the time of puberty. In patients with delayed puberty, great acceleration of growth is noted at the time of onset of genital growth. In young boys, chorionic gonadotropin stimulates the production of male sex hormone, and male sex hormone itself both produce striking stimulation of skeletal growth. Chorionic gonadotropin and male sex hormone both cause rapid ossification and ageing of epiphyses, and this effect appears to be counterbalanced by rapid increase in length of bone. Epiphyseal closure may be produced at an early age with sex hormones but there is no evidence that they alter the final height of the skeleton because the rapid increase in length may be counterbalanced by the epiphyseal closure.

The two influences of the pituitary on growth may be dissociated. Thus eunuchoid individuals are often normal in height, but their body proportions are abnormal. The sex hormones appear to be essential for the development of normal body proportions.

27. Clinical Experience with Ethinyl Estradiol

B. A. Watson. *Endocrine Clinic, Battle Creek Sanitarium, Battle Creek*

Twenty-one-months' experience in treating 18 menopause patients with ethinyl estradiol is presented. Average age was 48 years. Sex hormone assays were made on all patients preceding treatment. Average female sex hormone excretion per 24 hours was 4.5μg. of estrone; average excretion of 17-ketosteroids was 7.2 mg. of androsterone. Enteric coated and plain tablets were used and only one toxic reaction occurred, an urticarial reaction after only 0.25 mg. of the drug had been given in 4 days. This patient reported the same experience with stilbestrol. It was found that relatively small doses would produce relief of symptoms. Phenobarbital tablets, grains ½, were used during treatment as a control and symptoms returned. Ethinyl estradiol was used to replace parenteral therapy successfully, and effectiveness of the drug was confirmed in an adequate number of cases by vaginal smears. An ideal way of giving the drug to avoid toxic reactions is described. Detailed records of five patients are shown because of their interesting experiences during treatment.

66. Sex Hormone Assays in the Male

B. A. Watson and L. Rauls. *Endocrine Clinic, Battle Creek Sanitarium, Battle Creek*

Summary and analysis of findings in 38 male patients who had male and female sex hormone assays are presented. The average age was 52.8 years (range 29–77). Average 24-hour excretions of 17-ketosteroids expressed in mg. of androsterone was 10.5 (range 3.9–24.5 mg.); average female sex hormones, expressed as μg. of estrone, was 5.3 (range 1.7–17.7μg). Seventeen had symptoms of the male climacteric including loss of libido and/or impotence. Average age was 52.7 years (range 37–64). Average 24-hour excretion of male sex

hormones was 9.5 mg. androsterone (range 4.9–22.5 mg.); female sex hormones 3.9μg estrone (range 2.4–16.6μg).

Further analysis of data shows no definite correlation between age and sex hormone excretions nor between severity of symptoms of the male climacteric and male and female sex hormone assays.

33. Treatment of Simmonds' Disease

Robert H. Williams and James L. Whittenberger. *Thorndike Memorial Laboratory, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston*

The present report concerns 5 cases of Simmonds' disease which have been treated with pellets of testosterone and desoxycorticosterone and with thyroid by mouth. The results have been highly gratifying. The diagnosis in these patients was established on the basis of the clinical picture with confirmation by the insulin tolerance test, electrolyte studies and estimation of the 17-ketosteroids and gonadotropins excreted in the urine. The pituitary pathology was thought to be chromophobe adenomata in 2 cases, postpartum necrosis in 2 and unknown in the other. All patients had had adrenal crises; in 3 cases the crises were severe. Two patients had spent most of the time in bed and all were inactive. Four patients had been treated from 1 to 12 years as cases of (primary) myxedema. Adrenal crises had been induced by the use of thyroid in each subject.

Assays were made in the hospital on each patient to determine the optimum amounts of testosterone and desoxycorticosterone necessary for implantation. Each patient changed from a vegetative organism to an active, energetic and happy individual. Particularly striking was the increase in strength which occurred. The blood pressure, weight, basal metabolic rate and serum sodium returned to normal and have remained there. Only a slight increase in the 17-ketosteroids of the urine occurred. No ill effects from the treatment have been observed except slight hirsutism in one female patient.

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